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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/607,156	06/29/2000	Marcel Loetscher	2225.1001-009	8374
21005	7590	02/25/2004	EXAMINER	
HAMILTON, BROOK, SMITH & REYNOLDS, P.C. 530 VIRGINIA ROAD P.O. BOX 9133 CONCORD, MA 01742-9133			ANDRES, JANET L	
			ART UNIT	PAPER NUMBER
			1646	

DATE MAILED: 02/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b> 09/607,156	<b>Applicant(s)</b> LOETSCHER ET AL.	
	<b>Examiner</b> Janet L. Andres	<b>Art Unit</b> 1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 10 November 2003.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 16,17,19-21 and 60-88 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 19-21,60,63,64,69-76,81-84,87 and 88 is/are allowed.
- 6) ☒ Claim(s) 16,17,61,62,65-68,77-80,85 and 86 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 29 June 2000 is/are: a) ☐ accepted or b) ☒ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                                   | 4) <input type="checkbox"/> Interview Summary (PTO-413)                     |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)               | Paper No(s)/Mail Date. _____  |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date <u>7/02</u> .  | 6) <input type="checkbox"/> Other: _____                                    |

### **RESPONSE TO AMENDMENT**

1. Applicant's amendment filed 10 November 2003 is acknowledged. Claims 16, 17, 19-21, and 60-88 are pending in this application. The text of those sections of Title 35, U.S. Code, not included in this action can be found in a prior office action.

#### ***Information Disclosure Statement***

2. Applicant states that no initialed copy of the second supplemental information disclosure statement has been received. Those references were considered and an initialed copy of the form 1449 is provided with this office action. Applicant further requests that the information provided in the third supplemental information disclosure statement be considered. Application 10/251686 has been considered; however, no form 1449 was provided. Similarly, application numbers 09/624594, 09/6335341, 09/633702, and 09/633799, listed in the second supplemental information disclosure statement, have been considered. If Applicant wishes the application numbers to appear on an issued patent, a separate form listing the application should be provided.

#### ***Drawings***

3. In order to avoid abandonment, the drawing informalities noted in the action of 19 December 2002 must now be corrected. Correction can only be effected in the manner set forth in the above noted paper.

***Claim Rejections Maintained***

4. The rejection of claims 16 and 17 under 35 U.S.C. 102(a) as anticipated by Marchese et al. is maintained for reasons of record in the office action of 2 July 2003 and newly applied to claim 85, which was erroneously rejected under 35 U.S.C. 103(a) in the previous office action.

Claim 85 depends from claim 16 and merely recites an additional property, that of increasing the concentration of intracellular free calcium, which would be inherent to a polypeptide substantially identical to that disclosed by Applicant. Thus this claim is correctly included in the rejection under 35 U.S.C. 102, for the reasons set forth below and in the previous office action.

Applicant argues that Marchese et al. al does not enable a protein consisting of the GPR9 amino acid sequence, because Marchese does not teach an initiator codon. Thus, Applicant argues, a protein consisting of the GPR9 amino acid sequence could not have been produced by expressing the nucleic acid disclosed in Marchese et al. Applicant further argues that, were such a protein chemically synthesized, it would not be able the have the claimed binding properties. Applicant argues that Marches does not teach how to fold the claimed protein. Applicant concludes that Marchese only discloses a theoretical sequence and does not enable the person of ordinary skill to make such a protein that binds IP-10 or Mig.

Applicant further argues that the GPR9 sequence is not substantially identical to the instant SEQ ID NO: 2 and that the Examiner's citation of Best and Spada, shifting the burden to Applicant, is improper. Applicant states that the person of ordinary skill knew that the N-terminus of the molecule is involved in ligand binding. Applicant cites Murphy et al. as teaching

the importance of the N-terminal region in determining the selectivity of binding. Applicant further cites Gerard et al. as teaching the significance of the acidic nature of the N-terminus.

Applicant's arguments have been fully considered but have not been found to be persuasive. To place a sequence coding for the protein of Marchese in an expression vector, with an initiating codon and signal sequence, and to express the resulting protein in a eukaryotic cell is well within the abilities of a person of ordinary skill in the molecular biological arts. Marchese further clearly identifies the encoded protein as a G-protein coupled receptor and compares its sequence to other such receptors known in the art. A truncation of only four amino acids, at the amino terminus and not affecting the characteristic membrane-spanning regions of a G-protein coupled receptor, would not substantially alter the properties of a protein with 365 amino acid residues. Such a protein, expressed by methods well known in the art, would fold correctly and exhibit the well-known seven transmembrane regions of a G-protein coupled receptor as readily as does the slightly longer sequence disclosed by Applicant. The Marchese reference is thus fully enabling for the disclosed GPR9 protein.

Applicant cites Murphy as teaching that the N-terminus is important in ligand determination. Applicant cites Murphy as teaching that differences between IL8RA, rabIL8R, and IL8RB cluster in the N-terminal segment, the e2 loop, and the C terminus. Thus Murphy compares proteins that differ in far more than the loss of four amino acids from an otherwise identical sequence. Furthermore, Murphy teaches that each of these proteins binds IL-8 (p. 613) and that two of them, IL8RA and rabIL8R, have very similar binding characteristics (p. 613). Thus, variations are tolerated in the IL-8 receptors without loss of binding of IL-8. Finally, Murphy also teaches that none of these proteins bind IP-10 or Mig. Thus, the teachings of

Murphy provide only generally guidance as to the properties of related receptors, and that guidance indicates that receptors that are far more divergent than GPR9 and instant SEQ ID NO: 2 maintain similar binding properties.

Applicant cites Gerard as teaching that acidic residues at the N terminus are part of the ligand-binding site. Applicant further cites Gerard as teaching that the third extracellular loop contains structures critical for ligand binding.

Marchese in fact states that GPR9 contains an “abundance of acidic residues...in the N terminus of the receptor encoded by GPR9” (p. 340, column 2). Further, as stated above, the comparison of the IL-8 receptors indicates that variation is tolerated while maintaining IL-8 binding.

Applicant has concluded, based on the teachings of Murphy and Gerard, that the protein taught by Marchese et al. as GPR9 is not substantially identical to instant SEQ ID NO: 2 and thus it is legally improper to shift the burden to Applicant to prove that its binding characteristics are different. However, for the reasons set forth above, that GPR9 differs from SEQ ID NO: 2 by only four N-terminal amino acids, that it contains the acidic residues taught by the art as being important for ligand binding, and that the comparison among the IL-8 receptors provides only general guidance and that guidance indicates that variation is tolerated, it is maintained that GPR9 and SEQ ID NO: 2 are substantially identical. The protein taught by Marchese et al. would inherently bind Mig and IP-10 and increase free calcium. Thus Marchese et al. anticipates claims to proteins that bind IP-10 or Mig, increase intracellular free calcium, and are encoded by polynucleotides that hybridize under stringent conditions to the complement of SEQ ID NO: 1.

5. The rejection of claims 61, 62, 65-68, 77-80, and 86 under 35 U.S.C. 103(a) as unpatentable over Marches et al. in view of Sambrook et al. is maintained for reasons of record in the office action of 2 July 2003.

Applicant argues that Marchese does not enable a person of skill in the art to produce a protein consisting of GPR9 and does not disclose that the protein binds a chemokine. Applicant thus argues that the Marches reference does not teach how to produce a fusion protein. Applicant further argues that the protein would not inherently bind IP-10 and Mig and that "obviousness cannot be predicated on what is unknown". Applicant concludes that even if a person skilled in the art were motivated to produce a fusion protein such a person could only have hoped that it might bind an as yet unidentified ligand.

Applicant's arguments have been fully considered but have not been found to be persuasive. As stated above, to produce a GPR9 protein is well within the abilities of one of skill in the molecular biological arts. To produce fusion proteins is equally within the abilities of the artisan; Sambrook provides the means for doing so. Such fusion proteins would inherently have the binding features disclosed by Applicant, for the reasons set forth above. It is not necessary that the artisan be aware of these binding features to be motivated to make fusion proteins, however. As stated in the office action of 2 July 2003, Marchese et al. teaches on pp. 343-344 that it is desirable to identify ligands, structural features, and functions of GPR9 and Sambrook provides the means to do so. Thus, Marchese teaches a protein that would inherently have the binding features disclosed by Applicant, for the reasons set forth in paragraph 4 above, and a fusion protein would also inherently have these features. Together, Marchese and Sambrook provide teachings sufficient to make such proteins. Motivation is provided by the statements of

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Marchese that it is desirable to investigate the properties of GPR9 and does not require knowledge of the inherent binding feature disclosed by Applicatn.

CLAIMS 16, 17, 61, 62, 65-68, 77-80, 85 AND 86 ARE REJECTED. CLAIMS 19-21, 60, 63, 64, 69-76, 81-84, 87, AND 88 ARE ALLOWED.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet Andres, Ph.D., whose telephone number is (571) 272-0867. The examiner can normally be reached on Monday through Friday from 8:00 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, Ph.D., can be reached at (571) 272-0871. The fax phone number for this group is (703) 872-9306. Communications via internet mail regarding this application, other than those under U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [yvonne.eyler@uspto.gov](mailto:yvonne.eyler@uspto.gov).

All Internet email communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark Office on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.




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Janet Andres, Ph.D.

February 23, 2004

  
JANET ANDRES  
PATENT EXAMINER